

Commentary

Carcinogen Risk Assessment

by Roy E. Albert*

A molecular biological rationale for the linear nonthreshold dose-response pattern for carcinogenesis is presented based on the mutagenic activation of oncogens as the basis of initiation. The approach assumes that the linear nonthreshold dose pattern at very low doses applies only to tissues that are promoted by intrinsic and extrinsic agents other than the one being modeled, and that risk is characterized on a relative rather than absolute basis in terms of aggregate tumor response.

Since this symposium is in honor of Norton Nelson I want to say a few words about him. I have known Norton Nelson for literally my entire professional life, going back 40 years when I was a cardiovascular fellow in the Department of Medicine with his war-time research buddy, the great Ludwig Eichna. Nelson recruited me in 1959 to the Institute, and I worked there over 20 years under his leadership. To put it in a word, he was a director of genius. The combination of a really powerful mind with an upbeat, forceful personality gave the Institute an intellectual glow that was a joy. It was greatly reassuring during all those years to know that the Institute was in the hands of someone who was, by far, the best in his field. His intellectual keenness, fund of knowledge, and grasp of an extraordinarily wide range of science was always a source of astonishment to me, and he was a model to emulate. As an administrator he was equally phenomenal with his ability to make decisions about complex matters almost instantly. I have never seen a better manager in terms of organizing complicated processes like the formulation of a NIEHS Center proposal. When you put all of this together in a person with a real depth of culture and a great talker you have the one and only Norton Nelson, the founder and guiding genius of the field of Environmental Health. It is not surprising that since his retirement as Director of the Institute he has been as busy as ever being an advisor to everyone on a galactic scale.

I would like to present some new ideas about carcinogen risk assessment. One of the things that I valued most in the years that I spent at this Institute under Norton Nelson was the freedom to pursue one's interest. In my case, it involved, amongst other things, the chairing the Carcinogen Assessment Group at the U.S. Environmen-

tal Protection Agency. This group developed virtually all of the methodology that is currently used in risk assessment at the federal and state level. The quantitative aspect of risk assessment involving dose-response relationships was taken over from the field of ionizing radiation. In the Atomic Energy Commission the risks, for example, of cancer of the thyroid and bone from radioactive fallout were estimated using a linear nonthreshold dose-response model. The rationale for this was that cancer must involve an irreversible genetic change and that mutation was a likely candidate. The dose-response relationship for radiation-induced mutations is linear, as is the case generally with chemical carcinogens. The linear nonthreshold dose-response model quickly became the dominant concept in quantitative risk assessment. This was because any dose, however small, had a calculable risk. The linear nonthreshold model has been, and still is, the only extrapolation model that is used generally.

Ironically, the Federal regulatory agencies have disavowed the mutational mechanistic basis for the linear nonthreshold dose-response model while continuing to use it. It is well recognized that the characterization of low-level dose-response patterns cannot be done by direct observation either in animal bioassays or in human epidemiologic studies. The confidence in the nature of the low-dose extrapolation model comes from its conformity to an understanding of carcinogenic mechanisms. To disavow the mechanistic basis for the single-hit linear kinetics and yet continue to use the model for risk estimation is not a very strong position.

The idea that the linear nonthreshold dose-response model might represent the initiation component of the two-stage initiation-promotion model occurred to my colleague Fred Burns and me several years ago, on the basis of experimental data that we developed dealing with dose-response in the two-stage mouse skin model. The dose response for graded doses of benzo(a)pyrene with a standard promotional pattern using the promoter phor-

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bol myristate acetate (PMA) was highly consistent with a linear nonthreshold dose-response pattern over three to four orders of magnitude of initiating dose (1). The same thing was true for the formation of BaP-DNA adducts in the mouse epidermis with graded single doses of BaP (2). We proposed the idea a few years ago (3) that the linear nonthreshold extrapolation might apply to only the initiation process rather than to complete carcinogenesis. The enthusiasm that greeted the notion was subliminal. However, the concept has revived with considerable force due to developments in molecular oncology. Of the various modes of activation of protooncogenes, namely, by insertion, amplification, translocation, and mutation, the mutational mode is the one that is highly consistent with a linear nonthreshold dose-response model. Moreover, the exciting finding was that the activation of *ras* oncogene by mutation generally of codon 61 or 12 is found in the early stage of the initiation promotion model in the mouse skin (4). In other words, the activated *ras* oncogene is found in papillomas brought out in skin by PMA initiated with a polycyclic aromatic hydrocarbon, and the activation of the *ras* oncogene persists from papilloma to carcinoma.

This sequence of benign tumors that eventually become malignant is characteristic of an initiation-promotion system, and it is seen in human colon cancer. Here, polyps develop that eventually progress to carcinomas. It has been observed that in lesions where the original polyp and the carcinoma are seen together, the activated *ras* gene is present in both, which is the same circumstance as seen in the mouse initiation-promotion skin model (5). All of this suggests that a single hit process, namely, activation of the *ras* protooncogene by mutation, could be the initiating lesion in the carcinogenic process.

This puts a rather novel twist to a view of the dose-response. It implies that at high doses there will be complete carcinogenesis. But, as the dose is diminished, the effect of the carcinogen is largely that of initiation because the promoting action fades away; whether tumors become manifest then depends on the amount of promotion present in the tissue from other sources. The implications are that there are two kinds of dose-response patterns: one in promoted tissues, where low doses will produce the sequence of benign to malignant tumors; and the other in nonpromoted tissues, where, as the dose of the agent is reduced, the formation of tumors simply disappears.

It seems reasonable that genotoxic agents that are carcinogenic at high doses are probably initiators at low doses. It is also possible that genotoxic noncarcinogens are also initiators at low doses and equally hazardous. This logic does not apply to nongenotoxic agents that are carcinogenic at high doses; it implies that the nongenotoxic carcinogens do not follow a linear nonthreshold model. Carcinogenic responses with genotoxic carcinogens at high doses does not mean that there will necessarily be any tumor response at low doses since this depends on the presence of promotion. It is, therefore, conceivable that the pattern of tumor responses would be different at high and low doses. As a hypothetical exam-

ple, liver and kidney tumors might form at high doses, whereas at low doses mammary tumors might dominate because of hormonal promotion; at low doses the occurrence of liver and kidney tumors could be absent because initiated cells in those organs are not promoted. One might expect that mammary tumors would occur at high doses as well as at low doses, but the occurrence at high doses could be partially concealed by a censoring effect of earlier tumor development in the liver and kidney.

The question arises as to how one recognizes promoted tissue. As a first approximation it may be those tissues that undergo episodic growth and involution by hormonal action or have an abnormally high cell proliferation rate due to disease processes such as gastric ulcers, colitis, osteomyelitis, or by the action of external agents that are toxic, such as alcohol on the upper gastrointestinal tract, cigarette smoke on the respiratory tract, infection of the cervix, or viral hepatitis, etc. Perhaps it is time to revive the old Virchow Chronic Irritation theory of cancer in a new form. Virchow's theory, which held sway for about 50 years until the 1930s, argued that chronic irritation with elevated cell turnover was the nonspecific and general cause of cancer. It might now be appropriate to think of Virchow's theory as a theory of promotion where the final common pathway for promoting agents is heightened cell proliferation. The initiation-promotion view of carcinogenesis would include initiation by carcinogens and spontaneous initiation (presumably as in the case of spontaneous animal tumors) and promotion by extrinsic chemicals, overnutrition, hormonal promotion, promotion by chronic viral infections, and chronic inflammatory processes as in autoimmune disease and possibly hyperproliferative states associated with tissue atrophy.

Drawing back from this cosmic view of cancer to the issue at hand, namely risk assessment, the position being advanced here is that low-dose risks from genotoxic agents are limited to promoted tissues. It is difficult to know exactly which tissues are going to be initiated by a given carcinogen, but this depends somewhat on the route of exposure. For example, it is clear that inhaled carcinogens such as *bis*-chloromethylether or formaldehyde react completely in the respiratory tract, whereas an inhaled agent like 1,3-butadiene that produces tumors in a wide variety of organs in mice would have to be regarded as a more diffuse carcinogen.

A simplified generalization would be to regard all tissues that show a background tumor occurrence as being promoted on the supposition that they must be promoted in order to develop tumors. The direct-acting agents with a high degree of reactivity would be localized to the organs of initial contact, while the others would be assumed to affect all tissues. It could be assumed that the aggregate tumor response induced in the animal would be translated to humans. Thus, the dose of 1,3-butadiene that causes a doubling of all tumors in the mouse would be assumed to double all tumors in humans. Agents that react only at initial sites of contact, such as formaldehyde, would be expected to have effects on background tumors only in that organ system in both animals and humans. For example, a formaldehyde exposure that doubles the

background occurrence of spontaneous tumors in the rat nose would be expected to do the same in the human nose; in addition it would be expected to increase the background tumor yield in humans lower in the respiratory tract: the nasopharynx, larynx, and tracheobronchial tree in relation to the amount of dose that reaches these parts. Extrapolation to doses below the doubling dose would be done on a linear nonthreshold basis because of the experimental evidence developed. What is proposed here is a relative risk approach, compared to the absolute risk method currently being used. The proposed approach also tends to break away from the painting-by-the-numbers mentality that is characteristic of current carcinogen-assessment thinking. It opens up the biological question of what is the basis for low-level carcinogenesis and whether the initiation-promotion model advanced here is valid; if so, how can the process be brought into sharper focus, e.g., to what extent do adducts of different types initiate cells in different tissues and how do the different classes of promoters interact with the ini-

tiated cells induced by the different kinds of genotoxic agents.

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